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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,533	05/26/2005	David J. Waxman	701586-52522	1019

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EXAMINER	
NGUYEN, QUANG	
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1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,533	WAXMAN ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-18,31-33,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-18, 31-33 and 37-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 01/31/08 was entered.

Amended claims 1, 3-18, 31-33 and new claims 37-38 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 102(b) as being anticipated by Bilbao et al. (WO 99/55382) was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(e) as being anticipated by Wilson et al. (US 2002/0131961 A1) was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(a) as being anticipated by Luo et al. (Human gene therapy 12:2191-2202, 2001; IDS) was withdrawn in light of Applicant's amendment..

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

New claim 37 recites the limitation "the non-replicating vector encoding the prodrug activating enzyme" in line 4 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because prior to this limitation, there is no recitation of any non-replicating vector encoding the prodrug activating enzyme. The only recitation of a vector encoding a prodrug activating enzyme is a replicating vector and not a non-replicating vector. Similarly, the limitation "the replicating vector encoding the apoptosis inhibiting agent" on lines 5-6 of the claim also lacks antecedent basis. Once again, prior to this limitation the only recitation in the claim is a non-replicating vector encoding an apoptosis inhibiting agent. The metes and bounds of the claim are not clearly determined. As written, it is unclear what exactly Applicants intend to claim, and therefore no prior art was applied.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1, 3-13 and new claim 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) for the same reasons already set forth in the Office action mailed on 8/8/07 (pages 6-10). ***The same rejection is restated below.***

Waxman et al disclose methods of killing neoplastic cells in both *in vitro* and in a mammalian patient, including a human patient, using NADPH-cytochrome P450 reductase (RED) gene transfer in combination with cytochrome P450 gene transfer to enhance the sensitivity of neoplastic cells to anti-cancer drugs that are activated by P450 enzymes, wherein the P450 gene and the RED gene are delivered using one or more viral vectors (e.g., retrovirus, adenovirus, and others), the cytochrome P45 gene is a mammalian gene such as P450 1A1, 1A2, 1B1, 2B1, 2B2, 2B4 and others and the P450-activated chemotherapeutic agent is cyclophosphamide (CPA), ifosfamide (IFA) or any other P450-metabolized chemotherapeutic drug (See at least Summary of the Invention, pages 7-14; page 40, lines 27-30). Waxman et al further teach that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines such as IL-2, IL-4 and IL-12 (page 12, first full paragraph). Waxman et al also teach targeting specificity for P450 and RED gene delivery is facilitated by "transcriptional targeting" including the

use of tumor-specific or tumor-selective DNA enhancer sequences (page 12, second full paragraph; page 31, first full paragraph). Waxman et al also disclose that although the viral genomes of the viral vectors used in the methods should be modified to remove or limit their ability to replicate, however, **replication conditional viruses** are also useful (page 33, line 27 continues to line 11 of page 34). Waxman et al also note that some therapeutic enhancement may also be anticipated in tumor cells with high levels of endogenous RED expression (page 55, lines 11-13); tumor cells transfected with both P450/RED genes (e.g., 9L/2B6/reducase cells) are themselves more chemosensitive and readily killed by CPA and IFA than others (see Fig. 15, and page 70, lines 12-13); current gene therapy technologies are limited by their inability to deliver prodrug activation or other therapeutic genes to a population of tumor cells with 100% efficiency and bystander cytotoxicity resultting when active drug metabolites diffuse or otherwise transferred from their site of generation within a transduced tumor cell to a neighboring, naïve tumor cell leads to significant tumor regression even when a minority of tumor cell is tranduced with the prodrug activation gene (page 3, lines 15-28).

Waxman et al do not teach methods of killing neoplastic cells further comprising the step of transducing neoplastic cells already transduced with a vector encoding a heterologous gene with a vector encoding an apoptosis inhibiting agent.

At the effective filing date of the present application, Bilbao et al already disclosed at least a method **to prolong or enhance transgene expression (up to 2 log increase)**, including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express

the Bcl-2 gene with the transgene in the same cell, due to the attenuation of expression of the transferred therapeutic gene based at least in part on loss of vector transduced cells in a variety of gene therapy applications (see at least the abstract; page 18, line 10 continues to line 3 of page 19; page 19, line 28 continues to line 5 of page 20; examples 26). Bilbao et al also taught specifically that at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach (page 2, lines 15-27). Bilbao et al further state that **"Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility"** (page 52, lines 6-10).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Waxman et al. by further comprising the step of transducing neoplastic cells already transduced with both P450/RED genes with a vector encoding an apoptosis inhibiting agent, such as Bcl-2, in light of the teachings of Bilbao et al.

An ordinary skilled artisan would have been motivated to carry out the above modification in order to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P450/RED genes and/or a transient delayed in the death of tumor cells tranduced with both P450/RED genes to produce or generate a more prolonged and higher concentration of cytotoxic drug metabolites to neighboring native tumor cells, a bystander cytotoxicity, that is known to lead to significant tumor regression. Bilbao et al already demonstrated successfully a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene

expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, and state specifically state that "Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility".

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 11/8/07 (pages 7-8) along with the Declaration of Dr. David Waxman filed on 11/8/07, have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the Examiner's analysis is directly contradictory to the approach of Dr. Waxman, because the Waxman reference teaches use of apoptotic agents not the use of anti-apoptotic agents. Therefore, an ordinary skilled artisan would not have been looking to Waxman reference to modify the Bilbao reference. In the Declaration, Dr. Waxman argued that the present invention requires transducing cells with an apoptosis inhibiting agent, and if one wishes to kill a cancer cell one would think

of using apoptotic inducing factors which are complete opposite of apoptosis inhibiting agents. The Waxman publication does not list any apoptosis inhibiting agents. Dr. Waxman further argues that based on the goal of cancer treatment using an agent what would prevent cell death would be counterintuitive. Dr. Waxman further argues that none of the Bilbao, Robertson and Beidler references is directed to treatment methods for cancer, and there would not have been any motivation to combine Waxman with Bilbao, Robertson or Beidler because this would have gone against what a skilled artisan knew about cancer therapies.

Firstly, please note that the above rejection is under 35 U.S.C. 103(a) and therefore each of the cited references does not have to teach every elements of the claims.

Secondly, please also note that the combined teachings of Waxman et al and Bilbao et al as set forth above **do not exclude** the use of an apoptotic factor such as an expression factor encoding p53 and/or a death receptor ligand Trail under control of a regulatable promoter; and they are not contradictory in any way to the goal of cancer treatment.

Thirdly, an ordinary skilled artisan would have been motivated to modify the teachings of Waxman et al. by further comprising the step of transducing neoplastic cells already transduced with both P450/RED genes with a vector encoding an apoptosis inhibiting agent, such as Bcl-2 in order **to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P450/RED genes and/or a transient delayed in the death of tumor cells transduced**

with both P450/RED genes to produce or generate a more prolonged and higher concentration of cytotoxic drug metabolites to neighboring native tumor cells, a bystander cytotoxicity, that is known to lead to significant tumor regression. Bilbao et al already demonstrated successfully **a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene expression**, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, and state specifically state that "**Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility**".

Fourthly, at the effective filing date of the present application in addition to the teachings of Bilbao et al, Luo et al. (Human gene therapy 12:2191-2202, 2001; IDS) already taught a method in which **coexpression of p35 (an apoptosis inhibiting agent) enhanced the inhibition of neointimal formation by Fas ligand via the utilization of Ad2/FasL/p35.** Additionally, Wilson et al. (US 2002/0131961 A1) also taught at least a method for gene transfer comprising the step of exposing a population of host cells in both *in vitro* and in a mammalian patient (e.g., hepatocytes, lung, muscle, epithelial cells) to **a recombinant viral vector which comprises a gene encoding an anti-apoptotic agent (e.g., Bcl-2) and a transgene (e.g., a transgene encoding a growth hormone, erythropoietin, factor IX, or liver enzymes such as ornithine transcarbamylase, arginase and others)**.

Accordingly, amended claims 1, 3-13 and new claim 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) for the same reasons set forth above.

Amended claims 14-18 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) as applied to claims 1, 3-13 and 38 above, and further in view of Robertson et al (US 6,709,866) and Griffith et al. (US 6,900,185) for the same reasons already set forth in the Office action mailed on 8/8/07 (pages 10-12). ***The same rejection is restated below.***

The combined teachings of Waxman et al. and Bilbao et al. were already presented above. However, none of the references teaches specifically the use of a vector comprising a nucleic acid encoding an apoptosis inhibiting agent operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis,, particularly p53 (elected species) expressed under control of a regulatable promoter, even though Waxman et al teach specifically that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines.

However, at the effective filing date of the present application Robertson et al already taught at least the use of a recombinant viral vector expressing various anti-

apoptotic polypeptides such as NAIP, HIAP, HIAP2, XIAP and other under the control of a regulatable promoter to inhibit death of a cell of the nervous system in a patient (see at least Summary of the Invention, particularly col. 3, lines 19-23; and cols. 20-22).

Additionally, Griffith et al already taught a method of inducing tumor cell apoptosis using Trail/Apo2-L gene transfer in a mammal, and optionally in combination with chemotherapeutic agents, radiotherapeutic agents or immune potentiating genes or proteins (see at least Summary of the Invention). Griffith et al further taught that Trail has an apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells (col. 1, lines 15-20). Griffith et al also disclosed that expression of Trail/Apo2-L gene is under the control of a promoter, including an inducible promoter or a tissue-specific promoter (col. 10, lines 1-16).

It would have been obvious for an ordinary skilled artisan to further modify the teachings of Waxman et al. and Bilbao et al., by also using a vector comprising a nucleic acid encoding an apoptosis inhibiting agent operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis,, particularly p53 (elected species) expressed under control of a regulatable promoter in light of the teachings of Robertson et al. and Griffith et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because the expression of an antiapoptotic gene and/or an apopotic gene under a regulatable promoter *in vivo* has been widely used and applied in various gene therapy applications as taught by Robertson et al. and Griffith et al. Additionally, the

expression of a transgene under a regulatable promoter can be turned on or off as needed or required by the treated patients. Furthermore, an ordinary skilled artisan would also have been motivated to select Trail/Apo2-L gene transfer to treat a mammal having a cancer due to its apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Robertson et al.; Griffith et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 11/8/07 (page 8) along with the Declaration of Dr. David Waxman filed on 11/8/07, have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants presented the same arguments as those for the rejection of claims 1, 3-13 and 38 above.

Please refer to the same Examiner's rebuttals to the same Applicant's arguments above.

Amended claims 1 and 3-6 **(with respect to the elected species p35)** are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) as applied to claims 1, 3-13 and 38 above, and further in view of Beidler et al. (J. Biol. Chem. 270:16526-16528, 1995) for the same reasons already set forth in the Office action mailed on 8/8/07 (pages 12-13). ***The same rejection is restated below.***

The combined teachings of Waxman et al. and Bilbao et al. were already presented above. However, none of the references teaches specifically the use of a vector comprising a nucleic acid encoding an apoptosis inhibiting agent which is p35. However, at the effective filing date of the present application Beidler et al. already taught that the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery because p35 inhibits TNF- and Fas-induced apoptosis, blocks the cleavage of PARP, a death substrate in the apoptotic pathway as well as blocking developmental, viral, and x-irradiation-induced cell death (see at least the abstract; page 16528, col. 1, last paragraph).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Waxman et al. and Bilbao et al., by also using a vector comprising a nucleic acid encoding an apoptosis inhibiting agent that is baculovirus p35 in light of the teachings of Beidler et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Beidler et al. already taught that the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Beidler et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 11/8/07 (page 8) along with the Declaration of Dr. David Waxman filed on 11/8/07, have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants presented the same arguments as those for the rejection of claims 1, 3-13 and 38 above.

Please refer to the same Examiner's rebuttals to the same Applicant's arguments above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633